

AD_____

GRANT NUMBER DAMD17-94-J-4261

TITLE: Effect of a Stress Reduction Intervention on Psycho-Immuno-Endocrine Parameters in Early Stage Breast Cancer

PRINCIPAL INVESTIGATOR: Ann O. Massion, M.D.

CONTRACTING ORGANIZATION: University of Massachusetts
Medical Center
Worcester, Massachusetts 01655

REPORT DATE: October 1997

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

19980416 160

QUALITY INSPECTED 4

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE October 1997	3. REPORT TYPE AND DATES COVERED Annual (30 Sep 96 - 29 Sep 97)	
4. TITLE AND SUBTITLE Effect of a Stress Reduction Intervention on Psycho-Immuno-Endocrine Parameters in Early Stage Breast Cancer			5. FUNDING NUMBERS DAMD17-96-1-4261	
6. AUTHOR(S) Ann O. Massion, M.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Massachusetts Medical Center Worcester, MA 01655			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Commander U.S. Army Medical Research and Materiel Command Fort Detrick, Frederick, Maryland 21702-5012			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200) This is a Career Development Award which provides salary support for research and training done under a separately-funded project, Grant Number DAMD 17-94-J-4475 (P.I. Dr. James R. Hebert), called the Breast Research Initiative for DetermininG Effective Skills (BRIDGES), which focuses on skills for coping with breast cancer, and consists of a prospective randomized intervention trial with women ages 65 or less, having stage 1 or 2 breast cancer, randomized to one of three arms: 1) a modified form of the University of Massachusetts Medical Center mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP); 2) a nutrition education program developed specifically for BRIDGES; and 3) a usual-care control group. Outcome parameters are: 1) psychological and behavioral indices of function and coping; 2) quality of life measures; 3) compliance with the interventions and medical treatment regimens; and 4) immunological/endocrinological measures consisting of cytokines and melatonin. Over the past year, I have been involved in the following aspects of the project: recruitment, providing part of the SR&RP intervention, writing manuscripts, serving on the Executive and Steering Committees, data analysis, and overseeing sample collection and analysis for the melatonin assays, quality control of the melatonin assay, first and second author of two book chapters related to the project, symposium presentation at the American Psychiatric Association annual meeting, and taking an introductory biostatistics course in the Dept. of Public Health.				
14. SUBJECT TERMS breast cancer; psychosocial intervention; meditation; relaxation technique; secondary prevention; nutrition; psychoneuroimmunology; quality of life.			15. NUMBER OF PAGES 22	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

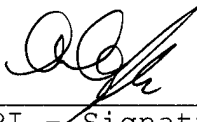
____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

✓ ____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

 m.D. 10-28-97

PI - Signature Date

TABLE OF CONTENTS

	<u>Pages</u>
Introduction	5-7
Statement of Work (revised as of 1996)	8-9
Work Accomplished	10-15
Conclusion	16
References	17
Appendices	
Abstract presented at the Society of Behavioral Medicine - March, 1997	18
Abstract presented at the American Psychiatric Association Annual Meeting (symposium) - May, 1997	19
Abstract of presentation at Univ. of Mass. Med. Center Breast Cancer Conference - September, 1997	20
Abstract to be presented at the Era of Hope Meeting - November, 1997	21 - 22

INTRODUCTION

This four-year Career Development Award provides me with salary support for a training practicum done as part of a separately funded research project, Grant # DAMD17-94-J-4475 titled "Effects of Meditation-Based Stress Reduction in Younger Women with Breast Cancer". The study is called the **Breast Research Initiative for DetermininG Effective Skills (BRIDGES)**, focusing on effective skills for coping with breast cancer. The Principal Investigator for that project, James R. Hebert, MSPH, Sc.D., is my mentor on the Career Development Award. Please note that my application for this award was originally written in association with another project application which was not funded. Therefore, the title for my DAMD # does not correspond with the title of the project listed under Dr. Hebert's DAMD #. The original Statement of Work was revised as part of last year's annual report in order to correspond with the work actually being done as part of the funded project. The section on Work Accomplished is structured according to the timeline for the project. The results of the project are included in Dr. Hebert's annual report. I have extracted portions of that report which apply to the work I have done.

Following is a summary of the background and overall goal for my Career Development Award. The background is extracted from the project grant. Also included are the specific aims and hypotheses from the project grant.

Background

An increasing body of research literature has shown that psychological states have clear impact on recovery and quality of life in women with breast cancer. Psychosocial variables such as emotional expression, coping style, and factors related to social support appear to have the most promise for improving quality of life and increasing the probability of prolonged survival. Also, there is a small body of evidence indicating that women with breast cancer receiving psychosocial interventions may derive a beneficial effect in respect to improved response and disease-free survival.

In light of these findings, there is an important need for the development of cost-effective psychosocial interventions for women with breast cancer. A successful intervention will be one that can reduce emotional distress, promote effective coping, and be useful and adaptable to the diverse population of women with breast cancer. The BRIDGES study seeks to adapt the University of Massachusetts Medical Center's Stress Reduction and Relaxation Program (SR&RP) for women with breast cancer. The SR&RP is a well-established intervention program with demonstrated effectiveness in improving emotional status and quality of life in individuals with a variety of serious medical problems. The program is educational in format. It has been offered to diverse populations, including a general hospital setting, an inner city clinic and a prison population.

The BRIDGES study addresses aspects of two of the fundamental research issues in psychosocial aspects of breast cancer: 1) the psychosocial impact of breast cancer, particularly on quality of life and ability to cope; and 2) identifying techniques for delivering cost-effective care to facilitate recovery, improve quality of life, and possibly improve immune response after receiving a diagnosis of breast cancer. The study is designed to evaluate the effectiveness of the SR&RP, previously untested in this population of patients, and compare it to a usual-care group as well as a nutrition education program which is an inactive attention control relative to the SR&RP but may have active therapeutic aspects as well.

Overall goal of the Career Development Award

My overall goal is to investigate a well-established short-duration psychosocial intervention, the University of Massachusetts Medical Center (UMMC) SR&RP for use with women with breast cancer. Outcome measures of particular interest are those relating to adjustment to illness, quality of life, ability to comply with medical recommendations, immune parameters related to tumor surveillance and potentially to the intervention, and an endocrine parameter, melatonin, which is believed to be an oncostatic agent involved in the immunological response to breast cancer and may potentiate the response to chemotherapy, thus representing a biologic predictor of good prognosis. My particular focus is on the psycho-physiologic interactions involved in coping with breast cancer, and on using the associated outcome measures to test the study hypotheses. This goal is achieved by working on the BRIDGES research project as a practicum experience. My mentor is Dr. James R. Hebert, the Project P.I. As noted above, the project is separately funded by your agency.

Specific Goals of the Career Development Award:

To gain experience and training in the following aspects of conducting this kind of research, which is a trial of a randomized psychosocial clinical intervention using psychosocial and biological outcome parameters: 1) research study design; 2) start-up planning; 3) recruitment; 4) delivering the intervention(s); 5) data collection and analysis; 6) hypothesis testing; and 7) reporting results via manuscripts.

Overall Goal of the BRIDGES study

The primary goal of this study is to test the efficacy of the well-established short-duration mindfulness meditation-based Stress Reduction and Relaxation Program (SR&RP) in women 65 years or less who have stage I or II breast cancer diagnosed within the past two years. The SR&RP intervention aims to influence a number of well-defined psychosocial factors which are suggested by a growing body of evidence as critically important for adjustment to a potentially life-threatening diagnosis: enhancement of quality of life and potentially enhancement of resistance to disease progression and survival in women with breast cancer. The study consists of a prospective randomized three-arm design with a target goal of 60 women enrolled into each arm: 1) the SR&RP intervention, tailored to focus on issues specific to breast cancer; 2) a nutrition education program which will serve as an inactive attention control with regard to the psychosocial outcome measures and as a potentially active intervention with regard to effect on some outcome measures, such as immune parameters (see Aim 2); and 3) a usual-care control group.

Specific Aims and Hypotheses of the BRIDGES study

Aim 1: to test the effect of the SR&RP on quality of life (QOL), emotional awareness and expression, coping strategies and related perceptual and behavioral factors, and compliance with the intervention and medical treatment recommendations in women ≤ 65 years who have been diagnosed with Stage I or II breast cancer within the past two years. Because the SR&RP and NEP groups will have an equivalent time commitment and the NEP will provide none of the essential components of the SR&RP, we will be able to examine the effect of the SR&RP intervention as distinguished from non-specific group-therapist factors.

Primary Hypothesis: the SR&RP intervention will result in improved QOL and ability to cope, compared to either the NEP or usual care alone.

Secondary Hypothesis: the SR&RP intervention will result in : a) improved perception of self and self in relationship to the world, as measured by increased self-esteem, sense of coherence, and decreased loneliness; b) a corresponding reduction in mood disturbance (e.g., anxiety and depression); c) increased use of active-behavioral and active-cognitive coping strategies, as measured by the Dealing with Illness Coping Inventory; and d) increased compliance with treatment regimens as compared to usual care alone.

Aim 2: to test the relative effect of the SR&RP versus NEP and usual care on endocrine/immune parameters specifically related to cytokines that activate Natural Killer (NK) cells and melatonin levels, which may in turn affect the response to breast cancer. Because NK activity may be related to recurrence, we have previously shown that low-fat diets enhance NK activity (Hebert, 1990) and we have preliminary data that meditation may affect melatonin levels (Massion *et al.*, 1995). Therefore, we are particularly interested in the relative differences between the two intervention groups, SR&RP and NEP, relative to usual care alone.

Specific Hypothesis: Relative to usual care, the SR&RP intervention will be associated with enhanced immune responsiveness and enhanced melatonin levels in women with Stage I or II breast cancer enrolled in this study. This will be reflected by an increase in the production of cytokines, e.g. Interleukins 2 and 4, which activate NK cells, and Interferon, which activates macrophages, and melatonin levels as measured by the primary urinary melatonin metabolite, 6-sulfatoxymelatonin.

Aim 3: to determine if the study effects (described in Aims 1 and 2), along with maintenance of the intervention practices, persist over 1-2 years of follow-up.

Specific Hypothesis: psychosocial and immunological changes will be maintained over time and related to on-going practice of the SR&RP self-regulatory strategies and behaviors, and NEP dietary practices.

REVISED STATEMENT OF WORK - this is the revised Statement of Work submitted with my 1996 annual report. I am including it here since the section on "Work Accomplished" is organized around it.

Task One: Run-in Phase, Months 1-3

- a, Conduct additional focus groups and preliminary data as needed. Analyze preliminary data previously gathered in support of this study.
- b. Based on focus group interviews and preliminary studies, the existing SR&RP intervention will be adapted and expanded so that the content of the program will be most useful to women with early stage breast cancer.
- c. Participate in finalizing and pilot-testing instrument materials.
- d. Develop the protocol for collection of 24-urine samples for the melatonin assays and for analyzing the results of the assay. Work with the laboratory technician who is performing the assays and the Project Director, Susan Druker, to ensure that transportation of specimens and the assay procedure will be operational. Using samples conducted for a preliminary study, test out the assay procedure. Work with Dr. Hebert and the study biostatisticians on data analysis of the results. This process includes developing a familiarity with the technical aspects of conducting this assay and possible confounding variables, such as oral agents which elevate melatonin levels.
- e. Participate in developing and creating the recruitment videotape and other recruitment materials (e.g. brochures) along with Drs. James Hebert, Judith Ockene, Jon Kabat-Zinn, and the Project Director, Susan K. Druker.
- f. Develop the recruitment protocol, along with Drs. Hebert, Kabat-Zinn, Clemow, and the Project Director, Susan Druker.
- g. Participate in training the Site Coordinators who will be conducting telephone and in-person interviews of the subjects. This will be done with Dr. Lynn Clemow, Co-Principal Investigator, and the Project Director, Susan Druker.
- h. Participate in setting up the database and analysis of run-in phase data, along with Dr. James Hebert and the biostatisticians on the project.

Task Two: Recruitment, Months 4-21:

- a. Serve as a member of the Executive Committee, composed of myself, Dr. Hebert, and Susan Druker, Project Director, to track the recruitment process and deal with any issues that may arise. Investigate any potential new recruitment sites as needed. This working group meets monthly to bi-monthly and functions to oversee the progress of the study, deal with administrative issues, and make decisions about issues that arise. An additional task will be to work on maximizing opportunities for recruiting subjects and improving the effectiveness of the process.

- b. Serve as a member of the Steering Committee, which meets quarterly and is attended by nearly all personnel involved in the study. These meetings are held to make some study decisions and maintain communication and cohesiveness among study personnel.
- c. Provide consultation and supervision as needed to Susan Druker and the Site Coordinators during the recruitment process.

Task Three: Intervention, Months 6-27

- a. Provide the six "booster" or "wrap-around sessions as part of the modified SR&RP intervention. These 6 sessions occur one before and five after the standard 8 week SR&RP program given at UMMC.
- b. Take a two-month internship training program in giving the SR&RP as an intervention. This is provided by the Stress Reduction Clinic at UMMC, under the direction of Saki Santorelli, EdD.
- c. Follow the progress of the nutrition education program (NEP) through the Executive and Steering committee meetings, where the nutritionist who gives the NEP will present progress reports.
- d. Continue to serve on the Executive and Steering Committees to deal with ongoing study decisions and issues.

Task Four: Follow-up, months 8-46

- a. Continue to oversee the melatonin sample collection and assay, as well as storage of samples, along with Susan Druker, Project Director.
- b. Participate in tracking ongoing data collection, validating the data according to each individual instrument, and begin preliminary testing of study hypotheses.
- c. As noted above, continue to oversee study progress by serving on the Executive and Steering Committee meetings, and being involved in administrative/study decisions.

Task Five: Final Data Analysis, months 47-51 (49-51 are a no-cost extension)

Along with Drs. Hebert and Clemow and the study biostatisticians, the following tasks will be done:

- a. Participate in performing exploratory analyses to test for adherence to model assumptions.
- b. Participate in testing study hypotheses.
- c. Participate in conducting post-hoc analyses of study data.
- d. Work with other study investigators and personnel in preparing manuscripts.

WORK ACCOMPLISHED

Task One: Run-in Phase, Months 1-3

a. Conduct additional focus groups and preliminary data as needed. Analyze preliminary data previously gathered in support of this study and in preparation for the study.

A preliminary focus group was conducted with a community-based breast cancer support group in order to gather data that would inform certain decisions such as timing of recruitment, and timing and length of the intervention itself. I conducted the focus group with another co-Principal Investigator. This data was then used in developing the recruitment protocol as well as the intervention protocol.

b. Based on focus group interviews and preliminary studies, the existing SR&RP intervention will be adapted and expanded so that the content of the program will be most useful to women with early stage breast cancer.

I was involved in the development of the modified SR&RP intervention, which consisted of adding 6 additional sessions, one session before and five after the standard SR&RP program which is 8 weeks long. The 8 sessions, provided as part of the standard stress reduction program already offered at the University of Massachusetts Medical Center, are larger groups composed of 30-40 people with a wide variety of medical or psychiatric problems, not just breast cancer. The 6 sessions were "wrapped around" the standard program and were given only to the women in the BRIDGES study. These were small group sessions composed of 6-12 women. The purpose of these sessions is to reinforce the practices taught in the program and give the women a chance to talk about issues specific to breast cancer.

c. Participate in finalizing and pilot-testing instrument materials.

I was involved in developing sections of the baseline questionnaire, particularly pertaining to medical and psychiatric information, as well as finalizing the acquisition and preparation of all of the psychosocial instruments for use in the study.

d. Develop the protocol for collection and of the 24-urine samples for the melatonin assays and for analyzing the results. Develop a familiarity with the technical aspects of conducting this assay and any possible confounding variables, such as oral agents which elevate melatonin levels.

I researched and developed the procedure for collection of 24-hour urine specimens, delivery of the specimens to the laboratory which is conducting the melatonin assays for the study, storage of specimens, and data analysis of the results. Also, I oversaw a trial run of assays which was conducted by the laboratory using samples from a preliminary study which I conducted with another co-investigator. This included working with the laboratory technician and Project Director to ensure that the assay procedure was feasible and to resolve any potential problems with it. I continue to oversee any issues which arise in relation to the assay and sample collection for it. This includes checking the results and monitoring for any factors which might confound the results (such as oral agents which elevate melatonin levels).

e. Participate in developing and creating the recruitment videotape and other recruitment materials (e.g. brochures), along with Drs. James Hebert, Judith Ockene, Jon Kabat-Zinn, and the Project Director, Susan Druker.

I attended weekly meetings during the first approximately 6 months of the study. The meetings were attended at various times by site coordinators from the four participating sites, the Principal Investigator, Project Director, and other investigators. I also chaired or participated in sub-committees involved in: 1) developing screening questions and baseline questionnaires to be used in recruiting and at the baseline assessment; 2) writing the script for the recruiting videotape and being involved in producing the videotape which was then used at the participating sites; 3) writing and producing other recruitment materials such as the brochure and descriptions of the individual interventions themselves; and 4) developing the actual recruitment procedure with specific modifications for each site.

f. Develop the recruitment protocol, along with Drs. Hebert, Kabat-Zinn, Clemow, and the Project Director, Susan Druker.

As part of developing the recruitment protocols, I researched the effectiveness of recruitment methods used in other studies similar to ours and contacted other investigators involved with those studies who were able to provide valuable information. I was part of a working group, composed of Dr. Hebert and the Project Director, Susan Druker, which developed the procedure for recruiting subjects at each of the study sites. I had the specific task of researching recruitment strategies which were specific for two of the sites, Medical Center of Central Massachusetts and Fallon Clinic. This involved interfacing with the various medical/surgical specialty clinics involved in seeing women with breast cancer, as well as the departments involved in keeping databases which could identify potential subjects for the study. I worked with Susan Druker on integrating all of the strategies for all the sites in the study.

Also, I was involved in developing the screening questionnaire used during the recruitment process.

g. Participate in training and supervising the Site Coordinators who will be conducting telephone and in-person interviews of the subjects. This will be done with Dr. Lynn Clemow, Co-Principal Investigator, and Susan Druker, Project Director.

I was involved in supervising and training Susan Druker and the Site Coordinators in developing the procedures for telephone and in-person interviews, along with Dr. Clemow. Also, I continue to be available for on-going consultation in screening and other clinical issues as needed.

h. Participate in setting up the database and analysis on run-in phase data, along with Dr. James Hebert and the biostatisticians on the project.

I have been involved in setting up the database and conducting process-related analyses (to ensure that data collections steps have occurred) and simple univariate analyses, under the supervision of Dr. Hebert and along with the study biostatisticians. I attend regular data analysis meetings to set up and develop the database and database management plan.

Task Two: Recruitment, Months 4-21

a. Serve as a member of the Executive Committee, composed of myself, Dr. Hebert and Susan Druker, Project Director, to track the recruitment process and deal with any issues that may arise. Investigate any potential new recruitment sites as needed. Work on maximizing opportunities for recruiting subjects and improving the effectiveness of the recruitment process.

I have performed this task as described above. These meetings will be ongoing throughout the study. One of the decisions made by the committee, after consulting with other study investigators, was to raise the age inclusion criteria to extend to women ages 65 or less. The rationale for this decision is explained in Dr. Hebert's report. Also, we extended the criteria for period of diagnosis to include women diagnosed within the past two years.

During 1995-1996 I explored options for other potential recruitment sites, particularly at three facilities in the nearby area. I was responsible for all of the initial contact work with the physicians and appropriate personnel at those facilities. I went with Dr. Hebert and the Project Director, Susan K. Druker, to make presentations at two of the facilities and meet with personnel who would be involved in recruiting. The two facilities, Burbank Hospital (an affiliate of UMMC and Bay State Medical Center in Springfield, MA., have agreed to informally recruit subjects for the study. The decision was made to leave the agreement informal rather than set up formal sub-contract sites.

178 women have been enrolled into the study, representing 99% of the recruitment goal (which was 180). Eighteen (10%) have dropped out of the study as of 10-1-97, representing a 90% retention rate. We estimated that our retention rate would be 80%. We feel our high retention rate is due to the positive response of our patients to this study, our recruitment methods, and the expertise of our Project Coordinator and site coordinators.

b. Serve as a member of the Steering Committee, which meets quarterly and is attended by nearly all personnel involved in the study. These meetings are held to make some study decisions and maintain communication and cohesiveness among study personnel.

I have been involved in planning and participating in quarterly Steering Committee meetings as described above. These meetings will be ongoing throughout the study.

Task Three: Intervention, months 6-27:

a. Provide the six "booster" or "wrap-around sessions as part of the modified SR&RP intervention. These 6 sessions occur one before and five after the standard 8 week SR&RP program given at UMMC.

During the first intervention cycle, I and another co-investigator provided the 6 "wrap-around" or booster sessions for the women randomized to the stress reduction intervention arm. Beginning with the second intervention cycle, I began providing the 6 sessions alone. These 6 sessions occur before and after the standard stress reduction program, as explained above. All six intervention cycles have been completed, each lasting 14 weeks total (8 standard sessions

plus 6 "wrap-around" sessions). In general, the women have been reporting that the intervention has been quite beneficial.

For quality control purposes, two senior instructors from the Stress Reduction and Relaxation Clinic, who teach in the 8-week program, sat in and observed some of the sessions provided by me in the sixth intervention cycle. They also reviewed audiotapes from two other sessions, also occurring in the sixth cycle. They met with me to provide comments and to discuss how the two segments of the intervention are integrated. In general, we have agreed that the integration has worked well and have been able to further conceptualize the model we are using.

b. Take a two-month internship training program in giving the SR&RP as an intervention. This is provided by the Stress Reduction Clinic at UMMC, under the direction of Saki Santorelli, EdD.

In 1996, I took a two-month training program in giving the SR&RP as an intervention.

c. Follow the progress of the nutrition education program (NEP) through the Executive and Steering committee meetings, where the nutritionist who gives the NEP will present progress reports.

I am aware of the progress of the nutrition education program (NEP) through the regular Executive Committee meetings and Steering Committee meetings, where the nutritionist who gives the NEP presents progress reports.

d. Continue to serve on the Executive and Steering Committees to deal with ongoing administrative study decisions and issues.

As noted above, these are ongoing meetings. The study is primarily administrated by virtue of the functioning of the Executive Committee, a working committee composed of myself, Dr. Hebert, and Susan Druker, the Project Director. Dr. Clemow and the study biostatisticians also attend as needed.

Task Four: Follow-up, months 8-46

a. Continue to oversee the melatonin sample collection and assay, as well as storage of samples, along with Susan Druker, Project Director.

This is being done as described. The assays are done in a batch when approximately 50 samples have been accumulated. I have been involved in quality control issues to maintain consistency and accuracy of the assay results and to insure that there is adherence to the assay protocol.

b. Participate in tracking ongoing data collection, validating the data according to each individual instrument and begin preliminary testing of study hypotheses.

Currently, I and other members of the research group are involved in validating the data according to each individual instrument to make sure that the data makes sense and is consistent. Also, along with Dr. Hebert and the study biostatisticians, I am involved in conducting descriptive, univariate data analyses and preliminary testing of study hypotheses

c. As noted above, continue to oversee study progress by serving on the Executive and Steering Committee meetings, and being involved in administrative/study decisions.

This is being done as described above.

d. Additional education

In September 1997, I began taking an introductory course in biostatistics at Univ. of Massachusetts, which will enhance my ability to participate in data analysis and testing of study hypotheses in this project. This is an additional activity which was not specified in the revised Statement of Work. I plan to take the second semester of this course in 1998.

Task Five: Final Data Analysis, Months 47-51

Along with Drs. Hebert and Clemow and the study biostatisticians, the following tasks will be done:

- a. Participate in performing exploratory analyses to test for adherence to model assumptions.
- b. Participate in testing study hypotheses.
- c. Participate in conducting post-hoc analyses of study data.
- d. Work with other study investigators and personnel in preparing manuscripts.

Because we are not yet at this stage of the study, the only activity has involved exploratory analyses and preliminary data which was used in manuscripts and presentations as follows:

Previously, I co-authored a paper reporting on preliminary data gathered prior to submitting the original grant application (Massion *et al.* 1995) in which we discussed one of the study hypotheses, namely that the SR&RP intervention would be associated with enhanced melatonin levels.

During 1996-1997, I was the first author of a second paper on another preliminary study conducted prior to the BRIDGES study, which related to and supported the same hypothesis. That study is in submission and has not been published yet.

During 1996, I co-authored two book chapters (first and second author), both of which discussed the BRIDGES study. The first chapter (Kabat-Zinn *et al.*, in press) discussed the use of the SR&RP intervention as an intervention for cancer patients. The chapter was primarily descriptive and briefly mentioned BRIDGES. No data was presented.

The second book chapter (Massion *et al.*, in press) discussed our hypothesis about meditation and melatonin. BRIDGES was discussed and preliminary data on melatonin levels from 82 subjects at baseline and 4-month follow-up (approximately 2-3 weeks after the intervention) was presented: crude mean difference for each group in μg per 24 hours, with the standard deviation of the difference (not the overall standard deviation) shown in parentheses was: SR&RP = +1.58 (11.87); NEP = +3.26 (9.03); and usual-care = -1.06 (10.30). Note that

the standard deviation of the difference is approximately $1\frac{1}{2}$ times as large as the standard deviation for the cross-sectional difference.

Due to the large variability in the data, the overall effect was not statistically significant ($p = 0.33$), nor was the effect due to either of the interventions relative to usual care: NEP ($p = 0.15$) and the SR&RP ($p = 0.34$). However, we believe the results are suggestive because they were obtained in a randomized trial where background factors are controlled by design and in which we would expect less of an effect than in a highly self-motivated group of experienced meditators - hence more relevance to the experience of average people. Also, these results were obtained on less than half of the projected sample and cover only the first four months.

Both chapters are still being edited and therefore are not included here.

I have been either first author or co-author for three 1997 presentations:

- a) co-author on paper presented at Society for Behavioral Medicine annual meeting in March, 1997 (abstract attached). This was a preliminary report ($n=75$) of baseline and four month scores on psychosocial measures.
- b) first author on symposium presentation at the American Psychiatric Association annual meeting in May, 1997 (abstract attached). This was a preliminary report of baseline and four month data on psychosocial measures for a subset of the total sample.
- c) co-author of presentation at breast cancer conference held at Univ. of Mass. Medical Center on September 23, 1997. This was presented by a co-P.I., Dr. Lynn Clemow, and involved presentation of preliminary data of baseline, four month and one-year data on psychosocial measures and dietary behavior, using a subset of the total sample.
- d) co-author of poster to be presented at "Era of Hope" meeting on 11-3-97, which will involve baseline and four-month data of a subset of the sample ($n=107$).

CONCLUSIONS

In general, my experience working on the BRIDGES study as a practicum for the Career Development Award has been excellent. I have been involved in a substantial portion of the project at every stage of progress, and have had direct impact on the majority of the major decisions and design issues. The training and experience I am receiving can be generalized to other clinical psychosocial interventions with psychosocial and biological outcome parameters.

As a group, we have been successful in recruiting 99% of our targetted total for subjects, with only 10% dropping out. The work accomplished has closely adhered to the Statement of Work outlined in the project grant.

REFERENCES

Clemow L, Hebert J, Massion A, Fowke J, Druker, S, and Thebarga R. A meditation-based stress reduction intervention for younger women with breast cancer. Paper session at Society of Behavioral Medicine annual meeting, March, 1997.

Kabat-Zinn J, Massion AO, Hebert JR, and Rosenbaum E. Meditation. In: Holland J (Ed.) *Textbook of Psycho-oncology*. London: Oxford University Press, In press 1998.

Massion AO, Teas J, Hebert JR. Meditation, melatonin, and cancer. In: Shafii M and Shafii S (Eds.). *Melatonin in Psychiatric and Neoplastic Disorders*. Washington, D.C.: American Psychiatric Press, Inc., In press 1998.

Massion AO, Teas J, Hebert JR, Wertheimer MD, and Kabat-Zinn J. Meditation, melatonin and breast/prostate cancer: hypothesis and preliminary data. *Medical Hypotheses* 1995; 44:39-46.

Massion AO, Hebert JR, Clemow L, Wertheimer MD, and Kabat-Zinn J. New research in psychosocial interventions for women with early-stage breast cancer: the BRIDGES study. Symposium presentation at the American Psychiatric Association annual meeting, May 19, 1997.

PA 19B

A MEDITATION-BASED STRESS REDUCTION INTERVENTION FOR YOUNGER WOMEN WITH BREAST CANCER

Lynn Clemow, Ph.D., James Hebert, Sc.D., Ann Massion, M.D., Jay Fowke, M.P.H., Sue Druker, M.A. University of Massachusetts Medical School, and Ron Thebarger, Ph.D., The Miriam Hospital/ Brown University Program in Medicine

This is a preliminary report (n=75) of an intervention for women <age 60 with Stage I or II breast cancer. Women were randomly assigned to one of 3 groups: 1) Stress Reduction group, based on the U. Mass. Stress Reduction and Relaxation Program, plus 6 group therapy sessions; 2) Dietary Intervention Group; and 3) Standard Care. The two group interventions have equivalent contact time, elements of group support, and are equally well-received by patients.

Comparisons were made between baseline scores on psychosocial measures and 4-months later (immediate post-treatment for the treatment groups), with repeated-measures ANOVAS. Significant ($<.05$) Group X Time interactions were found, showing an advantage for the stress reduction group on the following variables: Dealing with Illness Active/Cognitive Coping, and Avoidant Coping; the Spirituality scale of Quality of Life (as measured by FACT-B); and the SCL-90 hostility scale. In addition, in preliminary analyses, similar trends ($p=0.1$ or less) were found for physical and functional dimensions of Quality of Life and SCL-90-R scales measuring anxiety, depression, interpersonal sensitivity and overall distress (GSI). Overall, the measures suggest some specific beneficial effects of a psychological/stress reduction intervention over a credible group dietary intervention with younger women with breast cancer.

CORRESPONDING AUTHOR: Lynn Clemow, Ph.D. Behavioral Medicine, U Mass Medical Center, 55 Lake Ave N, Worcester, MA 01655

ogy. This review will discuss studies on the emotional consequences of the following tests specific to breast cancer: 1) risk assessment for the BRCA1 gene, 2) screening mammography, 3) follow-up testing for recurrence of disease.

Patients tend to overestimate the utility of screening and diagnostic tests, and often incorrectly perceive the significance of a "normal" test. Individual variations in coping style appear to be a key factor in determining different psychological responses to receiving information. Prospective evaluations of quality of life and patients' perceptions of diagnostic interventions are needed, as well as physician training to assess and address the specific psychological needs of patients.

No. 14B FERTILITY ISSUES IN WOMEN TREATED FOR BREAST CANCER

Randy S. Glassman, M.D., *Department of Psychiatry, Brigham & Women's Hospital, 75 Francis Street, Boston MA 02115*; Alison Fife, M.D.

SUMMARY:

For a woman of child-bearing age, a diagnosis of breast cancer carries both a physical and an emotional burden. The physical side effects of chemotherapy are numerous, and include potential effects on ovarian function, which affects fertility and sexual function, and may have implications for fetal anomalies. For example, female patients who have undergone bone marrow transplantation for acute myeloid leukemia have gone on to have successful pregnancies. Others developed ovarian failure and were unable to become pregnant. Infertility becomes an issue for these women, and carries with it the potential for comorbid psychological dysfunction for the patient, her partner, and family.

We review here the medical, ob-gyn, and psychiatric literature on fertility and the psychological and psychiatric issues in women who are anticipating or who have undergone treatment for breast cancer. The known effects of chemotherapy on ovarian function, and the available data on pregnancy outcomes will be reviewed. Additionally, the newer infertility treatments will be reviewed as they relate to decision making and psychological status. The potential for freezing embryos and possibly unfertilized eggs in the future will present women with new opportunities, but difficult and emotionally laden choices.

We will present information from interviews with women who have received chemotherapy for breast cancer, and who have either considered pregnancy or who have become pregnant. Psychiatric issues, comorbidity, and implications for treatment will be addressed.

No. 14C MEASURING DEPRESSION IN WOMEN WITH BREAST CANCER

Mary Jane Massie, M.D., *Department of Psychiatry, Memorial Sloan-Ketter, 1275 York Avenue, New York NY 10021-6007*; David K. Payne, Ph.D., Maria Theodoulou, M.D.

SUMMARY:

The most common types of psychological distress in women with breast cancer are depression and anxiety. Oncology staff members often ask consulting psychiatrists to recommend brief screening instruments that can be used to measure depression and anxiety and to assist them in learning how to rapidly identify patients most in need of psychiatric consultation. We have explored the use of two screening instruments (the Hospital Anxiety and Depression Scale [HADS] and a 100m visual analogue scale [VAS]) to measure psychological distress in 103 women with breast cancer and have ex-

plored correlations between patients' perceptions of their psychological distress and oncological staff members' perceptions of patients' psychological distress. The HADS tapped significant levels of distress that correlate with patients' subjective assessments of distress. The VAS correlated well with both the medical oncologist's and oncology nurse's ratings of the patients' distress, as well as with the HADS. The usefulness and limitations of brief screening measures to identify women with breast cancer who could benefit from psychiatric consultation will be described.

No. 14D NEW RESEARCH IN PSYCHOSOCIAL INTERVENTIONS FOR WOMEN WITH EARLY- STAGE BREAST CANCER: THE BRIDGES STUDY

Ann O. Massion, M.D., *Department of Psychiatry, University of Mass Medical Ctr, 55 Lake Avenue North, Worcester MA 01655*; James R. Herbert, Sc.D., Lynn Clemow, Ph.D., M.D. Wertheimer, M.D., Jon Kabat-Zinn, Ph.D.

SUMMARY:

An increasing body of literature indicates that coping skills and psychosocial function can have an impact on quality of life and possibly recovery for women with breast cancer. There is a need to identify effective coping skills and cost-effective psychosocial interventions to facilitate coping with breast cancer. The BRIDGES study at the University of Massachusetts Medical Center was designed to address these issues. The study involves randomization to one of three arms: a meditation-based stress reduction intervention, a nutrition education intervention, and an individual approach group, which essentially is a usual-treatment group. Inclusion criteria are stage 1 or 2 breast cancer, age 65 or less, and within two years of diagnosis. Outcome variables include psychosocial measures (coping skills, quality of life, anxiety, and depression) and biological measures (immunological consisting of soluble Interleukin-2 receptor, Interleukin 4, and Interferon-gamma; and endocrinological consisting of the urinary melatonin metabolite, 6-sulphatoxymelatonin).

The presentation will include a brief literature review and presentation of preliminary data from the BRIDGES study (baseline and 4-month follow-up).

No. 14E TREATING FAMILIES OF WOMEN WITH BREAST CANCER

Bonnie B. Greenberg, M.S.W., *Department of Social Work, Dana-Farber Cancer Institute, 44 Binney Street, Boston MA 02115*

SUMMARY:

Women being treated for breast cancer are faced with many challenges. Success in meeting these challenges is impacted by the reaction and involvement of the surrounding family/social system. This presentation will explore in detail the dimensions of family psychosocial assessment, unique breast cancer related issues, and appropriate psychosocial interventions.

A thorough, accurate assessment of the family's structure and dynamics is essential to effective intervention. Important areas of focus in assessing families with cancer include communication patterns, coping mechanisms, ability of members to support one another, individual and collective definitions of hope, potential role realignments, and pre-existing areas of family stress.

Family interventions should include the spouse/significant other, children, and/or parents/extended family, as much as is logistically possible. Treatment needs to be tailored to both the unique issues and developmental stages of the individual members as well as the

Dr. Lynn Clemow

The Effects of a Meditation-Based Stress Reduction Program
in Women with Early-stage Breast Cancer

Lynn Clemow, Ph.D.

for the BRIDGES Study Group, James Hebert, Sc.D., PI

The Breast Research Initiative for determining Effective Strategies (BRIDGES) for coping with Breast Cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program and an attentionally equivalent Nutrition Education Program (NEP) on quality of life, a variety of psychosocial factors, dietary intake, melatonin, excretion, and circulating levels of cytokines. Recruitment ended in December, 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (under age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Results presented here are the psychosocial and nutritional data, based on data from the entire sample who completed the 4-month assessment, and a series of the first 97 participants for whom we have 1-year assessments.

Overall thus far, the SRC intervention appears to produce improvements in a number of psychosocial factors. The no-treatment control group (UC) appears to be associated with a slight deterioration and the NEP produces results intermediate between the SRC and UC. These variables (from the 4-month data) include Active Cognitive Coping ($p=.005$), Spirituality ($p=.0007$), Beck Depression scores ($p=.02$), as well as several indices of emotional distress measured by the SCL-90-R, including anxiety ($p=.04$), Depression ($p=.01$), Hostility ($p=.01$), and the overall emotional distress scale ($p=.01$). Many of these beneficial differences hold up significantly at 1-year, as well.

Large dietary changes were confined to the NEP: for example, there was a reduction of 7.2% of energy as fat in the NEP vs no change in either the SRC or the UC ($p<0.001$). Though not meant to be a weight loss program, the NEP was associated with a loss of 1.59 kg ($p=0.02$). This corresponds to a decrease in body fat equivalent to about 120 kcal of total dietary energy per day (about 60% of the reduction in total energy reported).

Results were consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the relevant psychological variables.

THE EFFECTS OF A MEDITATION-BASED STRESS REDUCTION PROGRAM IN WOMEN WITH EARLY-STAGE BREAST CANCER

Dr. James R. Hebert, Dr. Ann O. Massion, Dr. Lynn Clemow, Mr. Jay H. Fowke, Ms. Susan K. Druker, Dr. Judith K. Ockene, Dr. Jon Kabat-Zinn

University of Massachusetts Medical School
55 Lake Avenue, North, Worcester, MA 01655

The Breast Research Initiative for DetermininG Effective Strategies (BRIDGES) for coping with breast cancer is a 51-month randomized multi-center trial to test the effect of the UMass Stress Reduction Clinic (SRC) program on quality of life, a variety of psychosocial factors, dietary intake, melatonin excretion, and circulating levels of cytokines. The three-arm study also consists of a no-treatment control group (UC) and a Nutrition Education Program (NEP), attentionally equivalent to the SRC and designed specifically for BRIDGES. The NEP excludes all aspects of meditation that form the basis of the SRC but includes aspects of group support, education, and dietary change that could influence some or all of the outcome variables. Recruitment ended in December 1996 with a total of 178 subjects, 99% of the recruitment goal of 180 younger women (to age 65 years) newly diagnosed with early-stage (I or II) breast cancer, and a retention rate >90% thus far. Subjects were randomized in equal numbers to each of the three study arms. Randomization was blocked by: stage of disease (I or II); age (<45, 46 to 52, or 53 to 65 years); and medical center. The last of six intervention cycles of the NEP and SRC were completed in April of 1997.

Data on study outcomes and a number of relevant background factors and potential confounders or effect modifiers of intervention effects were collected at baseline, 4 months (just after the end of the interventions), 12 months, and 24 months. Currently, we have data on 107 women who have completed the 4-month assessment point. Salient results are summarized in Table 1.

Keywords: Dietary Fat, Randomized Clinical Trial, Quality of Life, Affective Symptoms, Meditation

This work was supported by the U.S. Army Medical Research and Materiel Command under DAMD17-94-J-4475 and DAMD17-94-J-4261.

Table 1: Summary of Changes by Intervention

Psychosocial Variables:	UC		NEP		SRC		p-values [†]			
	base-line	Δ*	base-line	Δ*	base-line	Δ*	Overall	UC vs NEP	UC vs SRC	NEP vs SRC
Active-Cognitive Coping (Dealing with Illness)	62.1	-2.7	62.5	0	62.4	+1.0	0.005	0.03	<0.001	0.43
Quality of Life (FACT-B)	118.9	-1.0	117.5	-0.2	111.2	+3.6	0.60	0.87	0.33	0.45
Spirituality	29.1	-1.5	27.4	-0.3	26.3	+3.4	0.004	0.58	<0.001	0.01
Depression (Beck)	7.7	-1.6	6.1	-0.3	8.9	-2.8	0.11	0.45	0.15	0.04
Sense of Coherence	155.5	-4.1	155.2	-2.6	148.2	+3.2	0.21	0.70	0.09	0.22
Hostility (SCL-90)	0.26	+0.09	0.23	-0.02	0.29	-0.11	0.03	0.13	0.01	0.31
General Symptom Index (SCL-90)	0.38	-0.03	0.30	-0.01	0.47	-0.13	0.42	0.89	0.22	0.31
Nutritional Variables:										
fat (g/day)	69.7	-1.7	80.8	-21.1	71.6	+2.7	0.05	0.08	0.51	0.02
fat (% of energy)	33.75	-0.26	35.28	-7.26	4.85	+0.87	<0.001	<0.001	0.34	<0.001
energy (kcal/day)	1825	-48	2064	-199	1826	-2	0.42	0.78	0.76	0.57
weight (kg)	69.59	0.48	72.51	-1.59	2.85	-0.27	0.02	0.006	0.28	0.08

* differences are the crude differences observed

[†] p-values are based on the difference adjusted for the baseline values

Thus far, the SRC intervention appears to produce an improvement in the psychosocial factors. UC generally appears to be associated with a slight deterioration, and the NEP is associated with results intermediate between the SRC and UC. As can be seen in the table, large dietary changes were confined to the NEP. Though the NEP was not meant to be a weight loss program, successful low-fat interventions usually result in some weight loss. The loss of 1.59 kg (3.51 lbs) in the NEP would correspond to a decrease of about 13.3g of body fat per day, the equivalent of about 120 kcal of total dietary energy per day (about 60% of the reduction reported).

Results are consistent with the hypothesis that the SRC meditation approach would affect a range of psychosocial variables. The NEP intervention not only produces impressive results in terms of dietary change but is associated with results intermediate between the UC and SRC on several of the psychological variables. There appears to be no effect of age on any study outcome, indicating that the effects of the interventions apply to older women in whom the incidence rate of breast cancer is the highest. Other studies have shown that effects of such interventions may increase over time. Therefore, there will be considerable interest in monitoring intervention effects at the one- and two-year time points. Results presented will extend and expand upon those shown here and we will discuss their implications.